Further Ex Vivo Evidence Supporting Higher Aspirin Dosing in Patients With Coronary Artery Disease and Diabetes

Kevin P. Bliden, MBA; Udaya S. Tantry, PhD; Joseph DiChiara, BS; Paul A. Gurbel, MD

Aspirin remains the cornerstone antiplatelet agent for primary and secondary prevention in patients with diabetes mellitus (DM), a disease associated with heightened platelet reactivity, endothelial dysfunction, and inflammation.1,2 Patients with DM are at a greater risk of death, myocardial infarction, and stroke resulting from thrombotic event occurrence than are patients without diabetes. Because reactive platelets play a central role in the genesis of thrombotic events, the antiplatelet effects of various antiplatelet therapy regimes have been a focus of ex vivo investigations in this high-risk population. The current guidelines recommend aspirin (75 to 162 mg QD) for primary prevention in men aged >50 years and women aged >60 years with diabetes at increased cardiovascular risk (10-year risk >10%). Despite these recommendations, the clinical efficacy of the widely used low-dose aspirin regimen (75 to 81 mg QD) to treat the patient with diabetes remains a major source of controversy, and the optimal dose is unknown.3

Previous investigations have examined the dose-related effects of aspirin on platelet reactivity. In stable patients with coronary artery disease (CAD), low-dose aspirin did not inhibit platelet function in a significant number, despite highly effective blockade of its primary platelet target cyclooxygenase-1 (COX-1).4,5 The ASPECT (Aspirin-Induced Platelet Effect) study, a double-blind, double-crossover, William design investigation of 81, 162, and 325 mg QD aspirin administered as single doses for 4 weeks, each over a 12-week period, was the largest serial pharmacodynamic investigation of the dose-related effects of aspirin on platelet function in patients with CAD.4 It was clearly demonstrated in the ASPECT study that aspirin inhibited platelet aggregation stimulated by agonists other than arachidonic acid in a dose-dependent manner; significant effects were observed for collagen- and shear-induced aggregation and 11-dehydrothromboxane B2 production. Dose-related inhibition of platelet aggregation was hypothesized to be due to effects of aspirin beyond inhibition of its primary target COX-1 by acetylation and was termed a non-COX-1 effect.4 In a post hoc analysis of ASPECT, patients with and without DM were compared. Greater platelet reactivity and a higher prevalence of aspirin resistance were present in the patients with DM. Aspirin doses of >81 mg QD (162 to 325 mg QD) were associated with similar rates of resistance and platelet function in patients with and without DM. It was hypothesized, therefore, that a higher aspirin dosing strategy than 81 mg QD in patients with diabetes may be associated with enhanced platelet inhibition and better protection against atherothrombotic event occurrence.6

Various mechanisms have been proposed to explain the attenuated antiplatelet effect of aspirin therapy in DM, such as reduced drug bioavailability, accelerated platelet turnover, and glycosylation of platelet membrane proteins.3 When platelet turnover is heightened, an increased proportion of large reactive platelets capable of protein synthesis are released from the bone marrow and can be identified as a marker of accelerated thrombopoiesis.7 Grove et al8 demonstrated an increased platelet turnover rate in DM by using flow cytometry to detect platelet RNA. The presence of COX-2 in immature platelets may contribute to aspirin-insensitive thromboxane A2 generation, as can the presence of COX-2 in leukocytes that participate in transcellular thromboxane A2 synthesis.9

In this issue of Circulation: Cardiovascular Interventions, Capodanno et al10 provide more evidence that aspirin doses >81 mg QD are associated with lower platelet function in stable patients with CAD and type 2 DM. The investigators sought to determine whether twice-daily aspirin dosing provided superior effects on platelet reactivity compared to once-daily dosing as demonstrated by others of increased platelet turnover in DM.7,8 By dosing twice instead of once daily, they hypothesized that lower platelet reactivity would result through improved inhibition of juvenile platelets. In a previous study by Addad et al,11 patients with DM treated with twice-daily dosing compared to once-daily dosing had lower platelet reactivity. Capodanno et al administered aspirin at the following weekly doses in succession to 20 patients: 81 mg QD, 81 mg QD, 162 mg QD, 162 mg QD, and 325 mg QD. Aspirin response was assessed by methods commonly used to assess the pharmacodynamic effect of aspirin: arachidonic acid-, collagen- and ADP-induced platelet aggregation; VerifyNow aspirin assay; and serum thromboxane B2. Three major results were reported: (1) dose-dependent effects on platelet function measured by collagen-induced aggregation, their primary end point, or by VerifyNow did not occur when aspirin was administered once daily; (2) twice-daily dosing was associated with lower platelet reactivity as mea-
sured by collagen-induced aggregation and VerifyNow; and (3) there was a dose-dependent effect on serum thromboxane B₂, levels irrespective of the frequency of dosing that did not correlate with platelet function measurements, most notably aggregation stimulated by arachidonic acid.

The aim of the current study is interesting and clinically relevant. However, some points must be raised and, in part, have been acknowledged by the authors. Platelet turnover was not assessed in the study. The demonstration of a relation between increased turnover and enhanced pharmacodynamic efficacy of twice-daily dosing would have strengthened the conclusion that “twice-daily administration of low-dose aspirin … is associated with enhanced platelet inhibition, likely by overcoming increased platelet turnover.” The type of aspirin administered was not specified. It has been reported that enteric-coated aspirin is associated with inferior antiplatelet effects compared to soluble aspirin. It has also been reported that concomitant proton pump inhibitor administration may affect the pharmacodynamic response to aspirin. Because 25% of the patients in the current study received proton pump inhibitors, a pharmacodynamic interaction, particularly after single daily dosing, cannot be excluded. Treatment duration may not have been sufficient to exclude potential crossover effects. A comparison of dosing effects in patients with and without DM, absent from the current study, may be a goal for future investigations.

Finally, there was no apparent difference in platelet function between 81 mg BID and 162 mg QD and between 162 mg BID and 325 mg QD. In the absence of differences in the pharmacodynamic effect between 81 mg BID and 162 QD and between 81 mg QD and 162 mg QD, the reported superiority of 81 mg BID versus 81 mg QD appears less certain. These data suggest that twice-daily dosing may not provide any additional antiplatelet effects versus once-daily dosing as illustrated in our interpretation of the Capodanno data in Figure A and B, which also provides a comparison with the DiChiara et al data.

The dose of aspirin that balances clinical efficacy and bleeding risk is unknown. Without question, thrombotic event rates remain high in patients with DM treated with the dosing regimens of aspirin used in clinical trials. The results of Capodanno et al that demonstrate an overall dose-dependent effect of aspirin on collagen-induced aggregation and thromboxane generation are supported by the analysis from the ASPECT study. In both studies, it appears that the greatest dose effect occurs between a total dose of 81 mg QD and 162 mg QD, where collagen-induced aggregation and thromboxane generation are most reduced. Thromboxane B₂ measured in the serum of clotted blood can result from a platelet source as follows: unblocked COX-1 in “old” and unblocked COX-1 and COX-2 in juvenile platelets and unblocked COX-2 in leukocytes through transcellular synthesis and, thus, not COX-1 specific. Furthermore, both studies largely demonstrated that no additional antiplatelet effects occurred by increasing the aspirin dose >162 mg QD, providing further ex vivo evidence that 162 mg QD may be the optimal aspirin dose in patients with CAD and DM. Whether splitting the dose is more effective will require confirmation in larger studies where platelet turnover also is determined. Twice-daily dosing has a sound rationale and is a further step in the quest to optimize the antiplatelet effects of the cornerstone therapy used in the high-risk patient with CAD and DM.

Disclosures
Dr Gurbel has received research grants from AstraZeneca, Bayer, Daiichi-Sankyo, Lilly, Portola, Pozen, and Sanofi-Aventis and consultant fees and honoraria from Accumetrics, AstraZeneca, Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, Lilly, Merck, Pozen Portola/Novartis, and Sanofi-Aventis. Mr Bliden and DiChiara and Dr Tantry have no conflicts to disclose.

References

Key Words: Editorials diabetes mellitus platelet aggregation aspirin dosing
Further Ex Vivo Evidence Supporting Higher Aspirin Dosing in Patients With Coronary Artery Disease and Diabetes

Kevin P. Bliden, Udaya S. Tantry, Joseph DiChiara and Paul A. Gurbel

Circ Cardiovasc Interv. 2011;4:118-120
doi: 10.1161/CIRCINTERVENTIONS.111.961847
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/4/2/118

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org//subscriptions/